Rapid Eye Movement Sleep Behavior Disorder and Potassium Channel Antibody–Associated Limbic Encephalitis

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Of six patients registered in our center with nonparaneoplastic limbic encephalitis associated with antibodies to voltage-gated potassium channels, the five men had rapid eye movement sleep behavior disorder (RBD) coincident with voltage-gated potassium channel antibody–associated limbic encephalitis onset. In three patients, immunosuppression resulted in resolution of RBD in parallel with remission of the limbic syndrome. RBD persisted in two patients with partial resolution of the limbic syndrome. Our findings suggest that RBD is frequent in the setting of voltage-gated potassium channel antibody–associated limbic encephalitis and can be related to autoimmune-mediated mechanisms. In addition, these observations suggest that impairment of the limbic system may play a role in the pathogenesis of RBD.

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Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by acting out altered confrontational dreams associated with the loss of REM sleep muscular atonia. The pathophysiology of RBD is thought to be mediated by dysfunction of the brainstem structures that generate REM sleep and its tonic and phasic motor components. This is based on studies in animals showing that selective lesions in the dorsolateral pons or in the medial medulla produce REM sleep without atonia associated with oneiric behaviors (see review by Schenck and Mahowald[1]). Moreover, RBD is common in neurodegenerative diseases involving the brainstem such as multiple system atrophy and Parkinson's disease,[2] and it has been described in subjects with focal brainstem lesions. In contrast, RBD has been reported in Morvan's chorea[3] and fatal familial insomnia,[4] two disorders not associated with brainstem impairment. This suggests that other areas of the brain may be implicated in the pathophysiology of RBD.

Voltage-gated potassium channel antibody–associated limbic encephalitis (VGKC-LE) is a potentially reversible autoimmune disorder characterized by memory impairment, confusion, and seizures.[5–8] To our knowledge, the association between VGKC-LE and RBD has never been reported. We identified one patient who experienced development of RBD coincident with VGKC-LE onset. Prompted by this observation, we evaluated whether RBD was present in the remaining subjects identified with VGKC-LE in our center.

Subjects and Methods

We looked for symptoms of RBD in six consecutive patients with VGKC-LE. Clinical diagnosis of RBD required a history of harmful or potentially harmful dream-enacting behaviors associated with unpleasant dream recall.[1] Confirmation of RBD by videopolysomnography required documentation of increased REM sleep tonic and/or phasic electromyographic activity associated with abnormal behaviors and absence of electroencephalographic (EEG) epileptiform activity.[1,2,9] Videopolysomnography was not available in two patients with histories highly suggestive of RBD. The sixth patient was a woman who lived alone, did not recall having dream-enacting behaviors or nightmares, and refused to undergo videopolysomnography.

Serum antibodies to VGKC were determined in Oxford, United Kingdom, as described previously.[7] Cerebrospinal fluid hypocretin-1 levels were tested, as described previously,[10] because all our subjects presented with hypersomnolence, hypocretin-1 deficiency occurs in anti-Ma2 encephalitis associated with hypersomnolence,[11] and RBD occurs in idiopathic narcolepsy.[1]

Results

We identified RBD in five male subjects with a median age of 65 years (Table). In all instances, VGKC-LE was characterized by progressive onset of short-term memory loss, confusion, and simple or complex partial seizures. None of the subjects had symptoms or signs suggesting brainstem involvement. Cancer did not develop in any subjects during the follow-up. All subjects presented with hypersomnolence, without cataplexy, hypnagogic hallucinations, or sleep paralysis that persisted after treatment of seizures and optimization of antiepileptic and other drugs that could cause somnolence. In all subjects, EEG showed epileptiform discharges in the

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Table. Characteristics of the Five Male Patients with RBD and VGKC-LE

Characteristic	1	2	3	4	5
Age at presentation (yr)	60	65	51	72	67
Interval between symptoms onset and treatment (wk)	18	12	2	24	4
Serum antibody VGKC level at disease onset (normal, <100 pM)	810	992	6254	1103	300
Serum antibody VGKC level after immunosuppression (normal, <100 pM)	<100	140	272	196	1145
CSF hypocretin-1 level at disease onset (normal, >200 pg/mL)	231	NA	139	257	287
Sodium at disease onset (mEq/L)	130	125	131	132	134
Immunosuppressor treatment	IVIG and steroids	IVIG and steroids	IVIG and steroids	IVIG	IVIG and steroids
Limbic encephalitis outcome after immunosuppression	Complete resolution	Complete resolution	Complete resolution	Partial resolution	Partial resolution
RBD outcome after immunosuppression	Complete resolution	Complete resolution	Complete resolution	No resolution	No resolution
Polysomnographic features of RBD	Yes	Yes	NA	NA	Yes
Submental tonic EMG before/after immunosuppression (%)	27.8/2.9	78/1.7	NA	NA	NA/88.0
Submental phasic EMG activity before/after immunosuppression (%)	24.6/3.8	17.5/4.9	NA	NA	NA/20.6
Four limb phasic EMG activity before/after immunosuppression (%)	25.2/0.5	14.6/0.3	NA	NA	NA/18.1
REM sleep before/after immunosuppression (%)	17/21	20/17	NA	NA	NA/41
REM sleep stages before/after immunosuppression (n)	5/3	6/4	NA	NA	NA/5
Follow-up (mo)	86	62	12	18	48

VGKC = voltage-gated potassium channel; CSF = cerebrospinal fluid; RBD = REM sleep behavior disorder; NA = not available; IVIG = intravenous immunoglobulin.

Patients 1, 2, and 5 were briefly reported in a previous series of VGKC-LE.[6] Initial PET scan in Patient 5 showed positive lymph nodes in the mediastinum suggestive of cancer. However, a second PET scan done 3 years later was normal. REM sleep EMG activity quantification methodology was described previously.[2,9]

temporal lobes during wakefulness, and magnetic resonance imaging (MRI) showed hyperintensity in the mesial temporal lobes on fluid-attenuated inversion recovery and T2-weighted image sparing the brainstem (Fig 1A). Blood tests showed high serum VGKC antibodies titers (median, 992pM; range, 300–6,254pM; reference, <100pM), absent onconeural antibodies, and hyponatremia. Cerebrospinal fluid hypocretin-1 levels tested in four subjects were normal in three (>200pg/ml) and intermediate in one (110–200pg/ml).[12]

Since the onset of the memory impairment, behavioral changes, and seizures, four patients (Patients 1–4) experienced dream-enacting behaviors while sleeping such as shouting and punching. Patients were unaware of their behaviors, but these behaviors were noticed by their wives several weeks before admission. If awakened, all four patients recalled fearful dreams such as being attacked by animals or persons. On admission, videopolysomnography confirmed in Patients 1 and 2 the occurrence of RBD showing increased REM sleep tonic and phasic electromyographic activity associated with excessive limb jerking and no EEG epileptiform activity (see Fig 1B). None of the four patients was treated with clonazepam or any specific therapy for RBD.

Patients 1, 2, and 3 were treated with antiepileptic drugs and cycles of intravenous immunoglobulin and steroids over 1 year. Shortly after the first cycle, there was a marked improvement of the neurological condition and seizures, but RBD symptoms persisted in all three patients. Completion of immunotherapy resulted in complete resolution of RBD symptoms, hypersomnolence, and limbic encephalitis features in all three patients (Fig 2A). In Patients 1 and 2, two consecutive videopolysomnographic studies performed 6 and 3

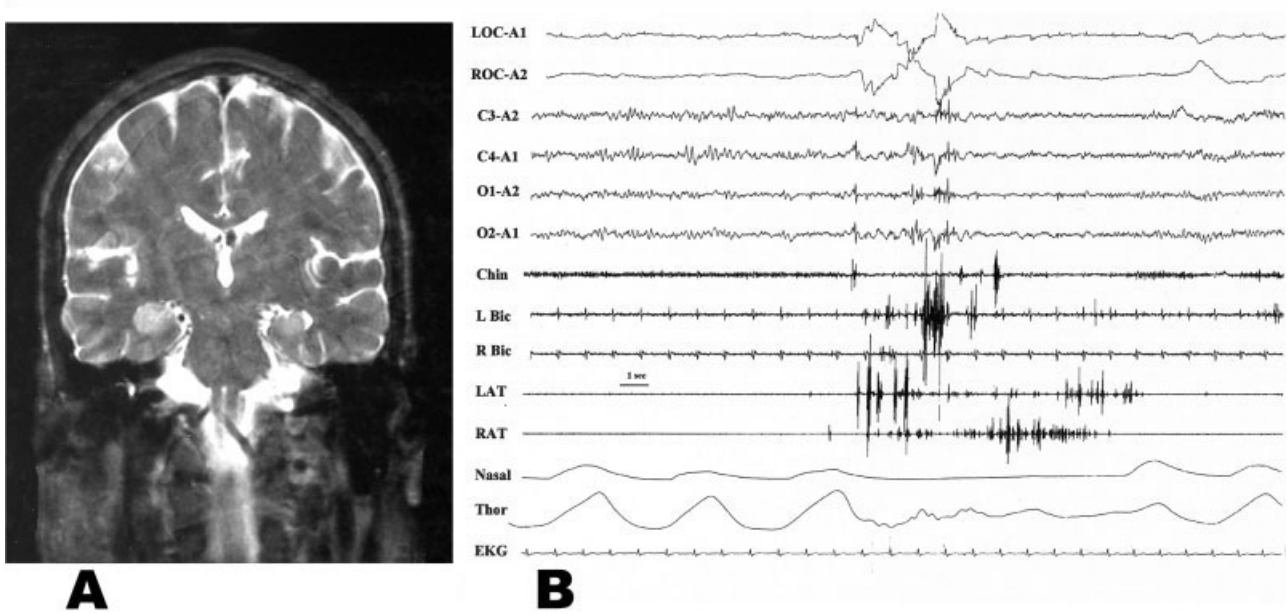

Fig 1. Patient 2 on admission; coronal T2-weighted brain magnetic resonance imaging shows bilateral, more pronounced on the right, mesial temporal hyperintensity sparing the brainstem (A), and polysomnography demonstrates increased phasic electromyographic activity in the limbs during rapid eye movement sleep (B). A = ear; C = central electroencephalogram (EEG); Chin = chin surface electromyogram (EMG); EKG = electrocardiogram; LAT = left anterior tibialis surface EMG; L Bic = left biceps surface EMG; LOC = left electrooculogram; Nasal = nasal airflow; O = occipital EEG; RAT = right anterior tibialis surface EMG; R Bic = right biceps surface EMG; ROC = right electrooculogram; Thor = thoracic breathing efforts.

years after disease onset confirmed the resolution of RBD showing restored REM sleep tonic and phasic electromyographic activity and no abnormal behaviors (see Fig 2B), together with substantial decreases in VGKC antibody titers.

Patient 4 started valproic acid and immunosuppression 6 months after the onset of limbic encephalitis and RBD symptoms. He received six cycles of intravenous immunoglobulin, without the addition of steroids, over 1 year. After 18 months of follow-up, seizures resolved, but despite reduction in VGKC antibodies, RBD symptoms persisted, memory loss and behavioral changes only slightly improved, and a second MRI showed no resolution of the limbic abnormalities.

Patient 5 received only two monthly cycles of intravenous immunoglobulin and methylprednisolone without great improvement and with persistent memory deficit and increased VGKC antibodies. His wife first noted dream-enacting behaviors such as gesturing and shouting 3 years after presentation of VGKC-LE and soon after starting fluoxetine because of apathy. During two months of fluoxetine therapy, the patient was unaware of his abnormal sleep behaviors, but recalled unpleasant dreams such as being kidnapped. Six months after fluoxetine withdrawal, videopolysomnography demonstrated RBD detecting REM sleep increased tonic and phasic electromyographic activity associated with limb jerking and no EEG epileptiform activity, and MRI showed bilateral hippocampal atrophy.

Discussion

Our study shows that RBD is frequent on the backdrop of VGKC-LE, and that some cases of RBD may have, as suggested previously,[13] an immune-mediated pathogenesis. In addition, our observations suggest that limbic system impairment may play a role in the pathophysiology of RBD.

To the best of our knowledge, this is the first study to show that RBD occurs in the setting of VGKC-LE. Interestingly, despite about 30% of sera with high VGKC antibodies being from women (A. Vincent and L. Clover, unpublished observations), both RBD and reported cases of VGKC-LE are predominately older men.[1,2,5–8] The high incidence of RBD found in our study may have been overlooked in previous reports of VGKC-LE. This is probably because physicians frequently pay less attention to sleep symptoms than to the dramatic symptoms occurring during wakefulness, such as confusion or memory loss, and because patients and bed partners did not spontaneously report these sleep disturbances. In fact, in four of our patients, a history consistent with RBD was detected only on specific questioning.

RBD usually occurs in the setting of neurodegenerative diseases, but no underlying cause has been identi-

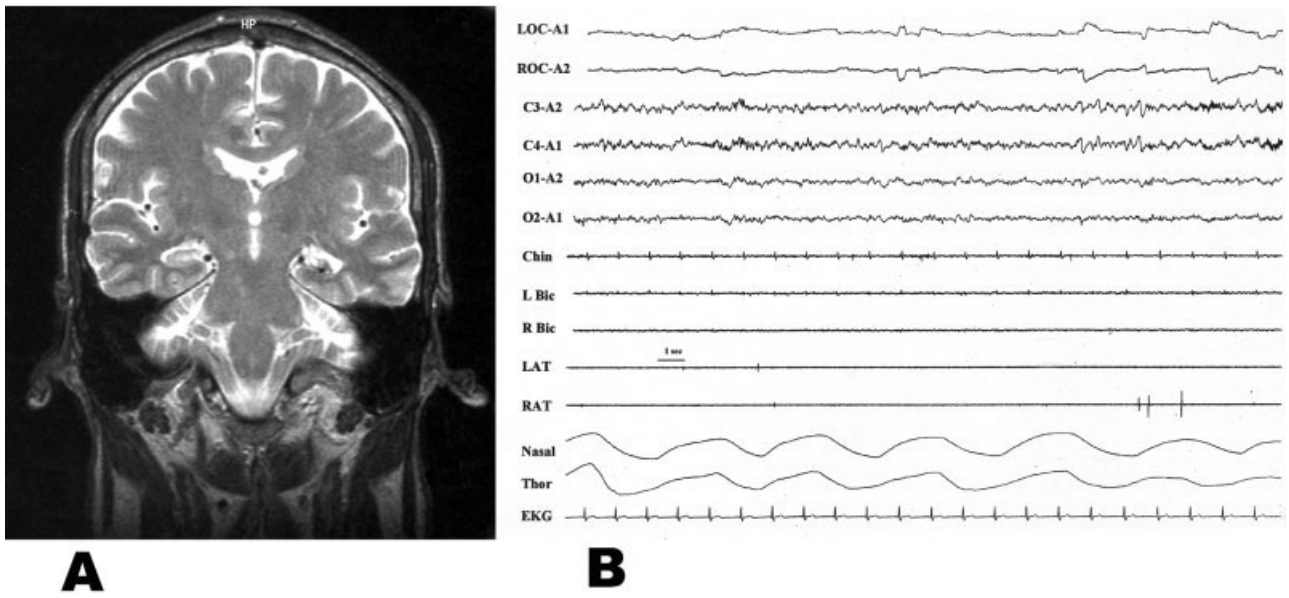

Fig 2. Patient 2 after immunosuppression; coronal T2-weighted brain magnetic resonance imaging shows resolution of the mesial temporal abnormalities (A), and polysomnography demonstrates normal rapid eye movement sleep without increased phasic electromyographic activity (B). A = ear; C = central electroencephalogram (EEG); Chin = chin surface electromyogram (EMG); EKG = electrocardiogram; LAT = left anterior tibialis surface EMG; L Bic = left biceps surface EMG; LOC = left electrooculogram; Nasal = nasal airflow; O = occipital EEG; RAT = right anterior tibialis surface EMG; R Bic = right biceps surface EMG; ROC = right electrooculogram; Thor = thoracic breathing efforts.

fied in the idiopathic form.[1,2] In four of our patients, there was a direct temporal association between development of RBD and LE syndrome linked to increased VGKC antibodies, and RBD responded to immunosuppression in three patients in parallel with remission of LE features. In our fifth patient, however, fluoxetine probably aggravated a mild form of RBD that may have existed since the onset of the VGKC-LE; fluoxetine and other serotonergic antidepressants are known to aggravate or induce RBD.[1,14] In three subjects, clinical impressions of RBD resolution or persistence were confirmed by quantification of polysomnographic REM sleep measures before and after immunosuppression (eg, tonic and phasic electromyographic activity and REM sleep consolidation).

None of our patients had cancer. Therefore, it is likely that, in our cases, RBD was caused by idiopathic autoimmune mechanisms related to VGKC antibodies. RBD also occurs in Morvan's chorea, another idiopathic autoimmune disorder associated with increased serum levels of antibodies to VGKC.[3]

It is accepted that RBD is caused by impairment of the brainstem structures that modulate REM sleep.[1,15] Our patients experienced RBD in parallel with limbic syndrome without any clinical or MRI evidence of brainstem involvement. There could, of course, be a direct pathogenic role of the VGKC antibodies within the brainstem because VGKCs are expressed widely in the brain.[16] Alternatively, a primary dysfunction of centers projecting to the brainstem, such as the limbic system, could be implicated in the pathogenesis of RBD.[1,15] Indeed, the limbic system, which mediates intense emotions during wakefulness, shows an intense metabolic activation during REM sleep that has been related to the important affective content of dreams,[17] and there are reciprocal strong anatomic connections between the limbic system and the brainstem regions responsible for REM sleep atonia.[15] Thus, dysfunction of the limbic system could account for the characteristic unpleasant dreams commonly recalled by the patients with RBD and the presence of excessive REM sleep motor activity leading to vigorous movements related to fearful dreams. In neurodegenerative diseases where RBD is frequent,[1,2] such as in Parkinson's disease, multiple system atrophy, and dementia with Lewy bodies, pathological changes in the limbic structures are common.[18–20] Moreover, in Parkinson's disease, there is marked damage to the mesolimbic dopaminergic system that originates in the substantia nigra and ventral tegmental area projecting to the limbic system.[18] Taken together, these findings suggest that, in our patients, the origin of RBD could be explained by primary damage of the limbic system leading to functional dysregulation of the brainstem REM sleep–related structures, and they suggest for the first time that the limbic system is directly involved in the pathogenesis of RBD.

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APOE ε4 Is Not Associated with Alzheimer's Disease in Elderly Nigerians

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Since 1992, research teams from Indiana University and the University of Ibadan have been collecting and comparing data from two diverse, elderly populations to identify risk factors for dementia and Alzheimer's disease. *Apolipoprotein E (APOE)* was genotyped in 2,245 Nigerian samples. Of these, 830 had a diagnosis: 459 were normal, and 140 had dementia including 123 diagnosed with Alzheimer's disease. In contrast with other populations, the *APOE* ε4 allele was not significantly associated with Alzheimer's disease or dementia. This lack of association in the Yoruba might reflect genetic variation, environmental factors, as well as genetic/environmental interactions.

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Alzheimer's disease (AD) is the most common form of dementia, accounting for a major part of public health spending in many developed societies[1] and be-

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